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Preparation and Screening of Some New Thioacetals, Sulfones, and Derivatives of 4-Dichloromethylbenzoyl and 4-Trichloromethylbenzoyl Chloride as Potential Antimalarials

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Abstract □ The preparation and screening of some potential antimalarials are reported. The new compounds which are inactive as antimalarials are several benzene-, benzyl-, and fluorene thioacetals, β-disulfones derived from these thioacetals, α-chlorobenzyl sulfones, amides, and thioesters derived from 4-dichloromethylbenzoyl chloride and 4-trichloromethylbenzoyl chloride. The known compounds bis(4-aminophenyl)sulfone and 4′-aminophenyl-4-aminobenzene thiolsulfonate also were prepared and showed some antimalarial activity.

Keyphrases □ Antimalarials—preparation of new thioacetals, sulfones, and 4-dichloromethylbenzoyl and 4-trichloromethylbenzoyl chloride derivatives □ Thioacetals—preparation of potential antimalarials □ Sulfones—preparation of potential antimalarials □ Derivatives—of 4-dichloromethylbenzoyl and 4-trichloromethylbenzoyl chloride, preparation of potential antimalarials

Malaria is still an important health problem in tropical areas. Various factors contribute to this situation including the development of malaria strains resistant to known antimalarials. This development has led to at least one recent antimalarial program (1). The purpose of the present work was to prepare potential antimalarials based on two model systems of known antimalarials, 1,4-bis(trichloromethyl)benzene which has been known as an active antimalarial for many years (2), and derivatives of bis(4-aminophenyl)sulfone which are more useful as suppressives than as therapeutic agents (3).

The synthesized compounds (Scheme I) share similarities with known antimalarials (2, 3). The trichloromethylaryl derivatives had no antimalarial activity, but the α-disulfone VIII*b* and the thiolsulfonate IX*b* showed some antimalarial activity.

RESULTS AND DISCUSSION

Thioacetals may be prepared by various methods (4–6) among which the reaction of *gem*-dihalides with sodium thiolates is a convenient one. Compound I*a* (Table I) was prepared from benzal chloride and a triethylammonium thiophenolate whereas VII*a* was formed easily from the *gem*-dihalide and a thiophenol. Acid-catalyzed reactions between 4-(trichloromethyl)benzaldehyde and various thiophenols gave the thioacetals I*c*, I*d*, and III*a*.

Two methods considered for the preparation of β-disulfones were a reaction of triethylammonium sulfinates with *gem*-dihalides or an oxi-

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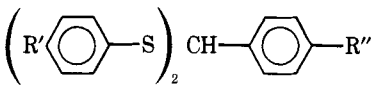
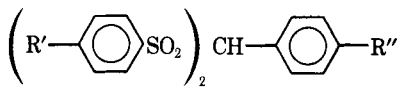
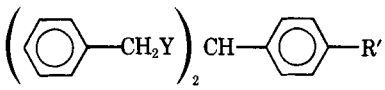


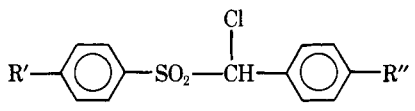
Ia: R′ = CH_3CONH, R″ = H
Ib: R′ = NH_3Cl, R″ = H
Ic: R′ = H, R″ = Cl_3C
Id: R′ = CH_3CONH, R″ = Cl_3C
Ie: R′ = NH_3Cl, R″ = CH_3OOC



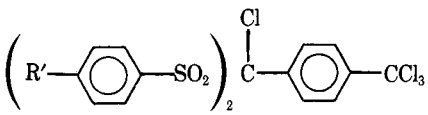
IIa: R′ = CH_3CONH, R″ = H
IIb: R′ = H_2N, R″ = H
IIc: R′ = H, R″ = Cl_3C
IId: R′ = CH_3CONH, R″ = Cl_3C
IIe: R′ = H_2N, R″ = Cl_3C
IIf: R′ = H, R″ = HOOC



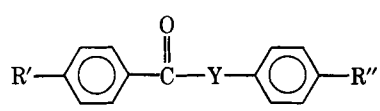
IIIa: Y = S, R′ = Cl_3C
IIIb: Y = SO_2, R′ = Cl_3C
IIIc: Y = SO_2, R′ = HOOC



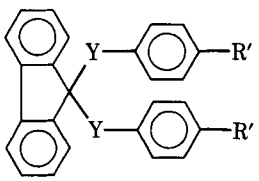
IVa: R′ = CH_3CONH, R″ = H
IVb: R′ = H_2N, R″ = H
IVc: R′ = H, R″ = Cl_3C



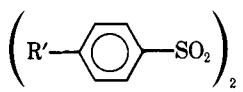
Va: R′ = H
Vb: R′ = CH_3CONH



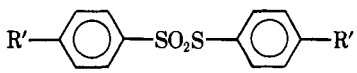
VIa: R′ = Cl_2HC, Y = NH, R″ = H
VIb: R′ = Cl_2HC, Y = NH, R″ = HOOC
VIc: R′ = Cl_2HC, Y = S, R″ = CH_3CONH
VId: R′ = Cl_3C, Y = NH, R″ = H
VIe: R′ = Cl_3C, Y = NH, R″ = NO_2
VIf: R′ = Cl_3C, Y = S, R″ = H
VIg: R′ = Cl_3C, Y = S, R″ = CH_3CONH



VIIa: Y = S, R′ = CH_3CONH
VIIb: Y = SO_2, R′ = CH_3CONH
VIIc: Y = SO_2, R′ = H_2N



VIIIa: R′ = CH_3CONH
VIIIb: R′ = H_2N



IXa: R′ = CH_3CONH
IXb: R′ = H_2N

Scheme I

dation of the thioacetals I, IIIa, and VIIa. However, only one of the halide atoms of benzal chloride was replaced by an aryl sulfinate and IVa was obtained, but only 9-fluorenone and water-soluble products were formed from 9,9-dichlorofluorene and the same aryl sulfinate. Oxidations of thioacetals with a solution of peracetic acid in dry methylene chloride yielded the corresponding β-disulfones in excellent yields, provided a large excess (12 molar equivalents) of the peracid was used. Reactions of the thioacetal Ia with the usual oxidation mixture, peracetic acid in acetic acid, yielded benzaldehyde and the known thiol sulfonate IXa. The formation of IXa most likely occurs *via* the *O*-protonated thioacetal *S*-oxide (7, 8). Such compounds are known to be extremely sensitive to acids and decompose to a resonance-stabilized sulfoxonium ion and a sulfenic acid. A nucleophilic attack by the sulfenic acid on the sulfoxonium ion will give a sulfenic ester which spontaneously fragments to form benzaldehyde and a disulfide (9), the latter being oxidized to the thiolsulfonate IXa. Alternatively, an attack by water on the sulfoxonium ion would give benzaldehyde and a thiophenol, which will lead to the thiolsulfonate *via* a sulfinic acid under these reaction conditions (10, 11).

Recently IXa was prepared (12) by the fragmentation of a benzenesulfonohydrazide by hydrochloric acid in acetic acid, with the arylsulfinic acid postulated as an intermediate.

Reactions of the β-disulfones IIc and IId with sodium hypochlorite gave chlorination of the α-methylene group and Va and Vb were formed, respectively. An attempt to prepare Va from the thioacetal Ic by chlorination using sulfuryl chloride, and subsequent oxidation of the crude product using peracetic acid in dry methylene chloride, resulted in loss of one sulfhydryl group, and compound IVc was obtained in good yield. Reactions of sulfides with sulfuryl chloride give various products depending on the reaction conditions; α-chlorination usually occurs (13), but recently thioacetals have been found to undergo *S*-oxidation by sulfuryl chloride in the presence of wet silica gel (14). Therefore, if the thioacetal Ic undergoes both *S*-oxidation and α-chlorination by sulfuryl chloride, the product IVc may be accounted for by a mechanism involving the formation of a sulfoxonium ion and simultaneous loss of a sulfenic acid.

Side-chain chlorinations of 4-methylbenzoyl chloride and 1,4-dimethylbenzene are to a large extent dealt with in the patent literature; a common problem to these reactions are mixtures of polychlorinated products which are not easily separated. However, 4-dichloromethylbenzoyl chloride was prepared in satisfactory yield by a peroxide-catalyzed chlorination of 4-methylbenzoyl chloride in carbon tetrachloride. The 4-trichloromethylbenzyl derivatives required the preparation of either pentachlorinated 1,4-dimethylbenzene or 4-trichlormethylbenzoyl chloride which could be reduced to the aldehyde. The radical chlorination methods reported previously (15–19) were unsatisfactory for the preparation of large quantities of these compounds. A zinc chloride-catalyzed chlorination of 1,3-benzenedicarboxylic acid by 1,4-bis(trichloromethyl)benzene[1] gave good yields of 4-trichloromethylbenzoyl chloride. Similar reactions were reported recently (20–24) but the objectives were to prepare various benzenedicarbonyl chlorides instead of 4-trichloromethylbenzoyl chloride.

1,4-Bis(trichloromethyl)benzene is an active antimalarial and various derivatives of this compound were prepared earlier (25). The prepared derivatives were tested[2] for activity in suppression of *Plasmodium gallinaceum* in the mosquito *Aedes aegypti*. The antimalarial test results showed that the chlorinated compounds were inactive but the previously known α-disulfone VIIIb suppressed the sporozoites completely in the mosquito salivary glands when administered in a 0.01% concentration of the mosquito feed. The only other compound which showed some antimalarial activity was the thiolsulfonate IXb. However, 4-trichloromethylbenzaldehyde showed activity earlier[3].

EXPERIMENTAL[4]

4-Methylbenzoyl Chloride—This was prepared from 4-methylbenzoic acid and thionyl chloride, bp_{36} 124–127° [lit. (26), bp_{36} 125°].

[1] Dr. R. F. Horvath, Research Department, Diamond Alkali Co., personal communication.

[2] Tests by Walter Reed Army Medical Center, Washington DC.

[3] National Institutes of Health, Cancer Research Department, Bethesda Md.

[4] IR spectra were recorded on a Perkin-Elmer 254 grating spectrometer. All melting points are uncorrected and were obtained on a Büchi "Tottoli" melting-point apparatus. Elemental analyses were carried out at Galbraith Laboratories. Peracetic acid (40%) was obtained from Becco. Raney nickel No. 28 was obtained from W. R. Grace & Co., and lithium tri-*tert*-butoxyaluminum hydride was obtained from Ventron Corp.

Table I—Thioacetals and β-Disulfones

Compound	Yield, %	Melting Point (Recrystallization Solvent)	Formula (mol. wt.)		Analysis, % C	H	Cl	N	S
Ia	81	189–190° (ethanol)	$C_{23}H_{22}N_2O_2S_2$ (422.58)	Calc.	65.37	5.25		6.63	15.18
				Found	65.40	5.09		6.70	15.29
Ib	85	224–225° dec. (acetonitrile–acetone)	$C_{19}H_{20}Cl_2N_2S_2$ (411.45)	Calc.	55.46	4.90	17.24	6.81	15.59
				Found	56.51	4.71	16.72	6.81	15.23
Ic	73	88–89° (heptane)	$C_{20}H_{15}Cl_3S_2$ (425.86)	Calc.	56.41	3.55	24.98		15.06
				Found	56.47	3.58	25.05		14.91
Id	45	169–170° dec. (acetonitrile)	$C_{24}H_{21}Cl_3N_2O_2S_2$ (539.97)	Calc.	53.38	3.92	19.70	5.19	11.88
				Found	53.51	4.09	19.78	5.30	11.85
Ie	90	218–219° dec. (ethanol)	$C_{21}H_{22}Cl_2N_2O_2S_2$ (469.50)	Calc.	53.73	4.72	15.10	5.97	13.66
				Found	53.66	4.65	15.09	5.82	13.35
IIa	95	259–260° dec. (*N,N*-dimethylformamide–water)	$C_{23}H_{22}N_2O_6S_2$ (486.58)	Calc.	56.78	4.56		5.76	13.18
				Found	57.03	4.72		5.80	13.65
IIb	53	205–207° dec. (acetone)	$C_{19}H_{18}N_2O_4S_2$ (402.51)	Calc.	56.70	4.51		6.96	15.93
				Found	57.03	4.95		6.63	15.42
IIc	88	222–223° (chloroform–benzene)	$C_{20}H_{15}Cl_3O_4S_2$ (489.86)	Calc.	49.04	3.09	21.72		13.09
				Found	49.18	3.19	21.90		12.87
IId	96	171° dec. (acetonitrile)	$C_{24}H_{21}Cl_3N_2O_6S_2$ (603.97)	Calc.	47.72	3.51	17.61	4.64	10.62
				Found	48.09	3.42	18.00	5.73	10.12
IIe	94	>300° (chloroform–tetrahydrofuran)	$C_{20}H_{17}Cl_3N_2O_4S_2$ (519.90)	Calc.	46.20	3.30	20.46	5.39	12.34
				Found	46.19	3.56	20.37	5.13	12.42
IIf	81	271–276° dec. (chloroform)	$C_{20}H_{16}O_6S_2$ (416.49)	Calc.	57.68	3.87			15.40
				Found	58.16	3.94			14.60
IIIa	65	89–90° (cyclohexane)	$C_{22}H_{19}Cl_3S_2$ (453.91)	Calc.	58.21	4.22	23.43		14.14
				Found	58.22	4.65	23.56		14.08
IIIb	92	250–251° dec. (chloroform)	$C_{22}H_{19}Cl_3O_4S_2$ (517.91)	Calc.	51.01	3.70	20.54		12.39
				Found	50.75	3.61	20.77		12.63
IIIc	41	247–249° (methanol)	$C_{22}H_{20}O_6S_2$ (444.54)	Calc.	59.44	4.53			14.43
				Found	59.68	4.47			14.68
Va	64	193–196° (carbon tetrachloride–cyclohexane)	$C_{20}H_{14}Cl_4O_4S_2$ (524.31)	Calc.	45.81	2.69	27.05		12.24
				Found	45.58	2.74	27.36		12.35
Vb	47	220° dec. (acetonitrile)	$C_{24}H_{20}Cl_4N_2O_6S_2$ (638.42)	Calc.	45.14	3.16			10.06
				Found	45.60	3.32			10.08
VIIa	89	209–210° dec. (acetonitrile)	$C_{29}H_{24}N_2O_2S_2$ (496.66)	Calc.	70.14	4.87		5.64	12.91
				Found	69.55	4.92		5.75	12.95
VIIb	83	272–273° dec. (tetrahydrofuran)	$C_{29}H_{24}N_2O_6S_2$ (560.66)	Calc.	62.13	4.31		5.00	11.44
				Found	62.11	4.49		5.03	11.52
VIIc	66	>290° (acetone–acetonitrile)	$C_{25}H_{20}N_2O_4S_2$ (476.59)	Calc.	63.00	4.23		5.88	13.46
				Found	63.22	4.30		5.94	13.03

4-Dichloromethylbenzoyl Chloride (X)—A carbon tetrachloride solution of 4-methylbenzoyl chloride was heated under reflux and chlorinated for 6 hr in the presence of catalytic amounts of benzoyl peroxide to give X (86%), $bp_{0.12-0.2}$ 88–93°, mp 43–59°; recrystallized from carbon tetrachloride, mp 45–47° [lit. (18) bp_{745} 285–286°, mp 44–45°].

4-Trichloromethylbenzoyl Chloride (XI)—A mixture of 1,4-bis(trichloromethyl)benzene (15.7 g, 50 mmoles), 1,3-benzenedicarboxylic acid (4.15 g, 25 mmoles), and zinc chloride (~200 mg) was protected from moisture. The mixture was heated at 185° for 4.5 hr until 95% of the 5% aqueous sodium hydroxide (40 ml, 50 mmoles) connected to the reaction flask was neutralized by the hydrogen chloride formed. The dark liquid reaction mixture was distilled under reduced pressure to give 14.2 g of a clear liquid, $bp_{0.4-0.45}$ 93–100°. This mixture of XI and 1,3-benzenedicarbonyl chloride was redistilled under reduced pressure on a polytef spinning band column and gave 1,3-benzenedicarbonyl chloride as the lower boiling fraction and 7.2 g (56%) of XI, mp 27.5–28.5°, $bp_{0.2-0.15}$ 88–91°; index of refraction, n_D^{25} = 1.5822, [lit. (18) bp_{756} 296°].

4-Trichloromethyl Benzaldehyde (27)—A stirred solution of XI (12.9 g, 50 mmoles) in 75 ml of dry tetrahydrofuran was cooled to −70°. A solution of lithium tri-*tert*-butoxyaluminum hydride (15.3 g, 60 mmoles) in 80 ml of dry tetrahydrofuran was added over 1.5 hr through a pressure-equalizing dropping funnel fitted with a polyethylene jacket filled with 2-ethoxyethanol and carbon dioxide. The reaction mixture was kept at −65° for 1 hr after all the reducing agent had been added, and for 15 min after ethanol (2 ml) had been added. The solution was poured onto a vigorously stirred mixture of 300 g of ice, 100 ml of 5% aqueous hydrochloric acid, and 100 ml of methylene chloride. The aqueous phase was extracted with another 100 ml of methylene chloride and the combined methylene chloride extracts were washed with 5% aqueous hydrochloric acid, aqueous sodium bicarbonate, and water, and were dried over magnesium sulfate. The residue, after filtration and removal of the solvent gave 11.1 g (99%) of 4-trichloromethyl benzaldehyde; IR (film): 1710 cm^{-1}.

An attempt to prepare 4-trichloromethyl benzaldehyde from VI*f* and Raney nickel (28) gave a mixture of VI*f* and 4-trichloromethyl benzaldehyde.

Peracetic Acid in Methylene Chloride—Solutions were prepared by extraction of 40% peracetic acid in acetic acid with four volumes of methylene chloride. The aqueous phase was removed and the organic phase was dried over magnesium sulfate. The strength of the peracid solution was determined by titration with 0.1 *M* sodium thiosulfate (29).

Thioacetals—*Bis(4-acetamidothiophenyl)phenylmethane* (*Ia*)—Triethylamine (12.1 g, 120 mmoles) was added to a solution of 4-acetamidothiophenol (20 g, 120 mmoles) and benzal chloride (9.65 g, 60 mmoles) in 120 ml of dry benzene. A second layer formed, and the two-phase solution was heated under reflux for 55 hr. The lower phase crystallized slowly. The crystalline material was filtered after cooling, stirred with water, and was recrystallized three times from ethanol to give I*a*; IR (mineral oil) 3300 and 1660 cm^{-1}.

Bis(4-aminothiophenyl)phenylmethane Dihydrochloride (*Ib*)—This was obtained by acid hydrolysis of I*a* in boiling methanol and hydrochloric acid.

Bis(thiophenyl)-4-trichloromethylphenyl Methane (*Ic*)—A solution of *p*-toluenesulfonic acid (~100 mg) in 80 ml of benzene was dried by heating to reflux under a Dean-Stark trap. The solution was cooled, the trap was drained, and 4-trichloromethyl benzaldehyde (50 mmoles, crude) was transferred into the reaction flask. Thiophenol (11 g, 100 mmoles) was added, and the reaction mixture was heated to reflux under a Dean-Stark trap for 3 hr. Approximately 500 mg (55.5%) of water was formed. The benzene solution was cooled and was extracted with two 50-ml portions of 2% aqueous sodium hydroxide, and two 50-ml portions of water and dried over magnesium sulfate. Compound I*c* was obtained from the benzene extract.

Bis(4-acetamidothiophenyl)-4-trichloromethylphenyl Methane (*Id*)—4-Acetamidothiophenol and 4-trichloromethyl benzaldehyde were used in the same procedure as described for I*c* except that chloroform was used as a solvent. Compound I*d* was recrystallized from acetonitrile; IR (mineral oil): 3300–3250, and 1680 cm^{-1}.

Bis(4-aminothiophenyl)-4-carbomethoxyphenyl Methane Dihydrochloride (*Ie*)—Compound I*d* was treated with boiling methanol and hydrochloric acid for 1.5 hr; IR (mineral oil): 1700 cm^{-1}.

Bis(thiobenzyl)-4-trichloromethylphenyl Methane (*IIIa*)—The method described for I*c* was used to prepare III*a* from thiobenzyl alcohol and 4-trichloromethyl benzaldehyde.

9,9-Bis(4-acetamidothiophenyl)fluorene (*VIIa*)—A solution of

Table II—α-Chlorobenzyl Sulfones and Benzoyl Derivatives

Compound	Yield, %	Melting Point (Recrystallization Solvent)	Formula (mol. wt.)		Analysis, % C	H	Cl	N	S
IV*a*	84	211–212° (tetrahydrofuran–ether)	$C_{15}H_{14}ClNO_3S$ (323.42)	Calc.	55.71	4.36	10.96	4.33	9.91
				Found	55.54	4.21	11.20	4.38	9.80
IV*b*	84	277–279° dec. (2-butanone)	$C_{13}H_{12}ClNO_2S$ (281.78)	Calc.	55.42	4.29	12.58	4.97	11.38
				Found	55.67	4.34	12.80	5.00	11.20
IV*c*	67	175–176° (cyclohexane)	$C_{14}H_{10}Cl_4O_2S$ (384.14)	Calc.	43.77	2.62	36.93		8.35
				Found	43.91	2.65	37.10		8.59
VI*a*	89	196–197° (tetrahydrofuran)	$C_{14}H_{11}Cl_2NO$ (280.17)	Calc.	60.02	3.96	25.31	5.00	
				Found	59.64	4.02	25.65	5.22	
VI*b*	88	>280° (acetone)	$C_{15}H_{11}Cl_2NO_3$ (324.19)	Calc.	55.58	3.42	21.88	4.32	
				Found	54.87	3.52	23.41	4.22	
VI*c*	90	216–217° (ethanol)	$C_{16}H_{13}Cl_2NO_2S$ (354.29)	Calc.	54.24	3.70	20.02	3.96	9.05
				Found	54.07	3.43	20.17	4.07	8.74
VI*d*	91	188–189° (acetone)	$C_{14}H_{10}Cl_3NO$ (314.62)	Calc.	53.44	3.20	33.82	4.45	
				Found	54.02	3.35	33.96	4.46	
VI*e*	72	210–212° (methanol)	$C_{14}H_9Cl_3N_2O_3$ (359.62)	Calc.	46.76	2.52	29.58	7.79	
				Found	46.96	2.64	29.46	7.73	
VI*f*	86	109–110° (cyclohexane)	$C_{14}H_9Cl_3OS$ (331.67)	Calc.	50.70	2.74	32.07	9.67	
				Found	50.66	2.82	32.31	9.71	
VI*g*	92	239–240° dec. (tetrahydrofuran)	$C_{16}H_{12}Cl_3NO_2S$ (388.74)	Calc.	49.44	3.11	27.36	3.61	8.25
				Found	49.67	3.24	26.75	3.62	7.82

9,9-dichlorofluorene (2.35 g, 10 mmoles) and 4-acetamidothiophenol (3.34 g, 20 mmoles) in 50 ml of dry acetonitrile was heated under reflux for 18 hr. Compound VII*a* was obtained after removal of the solvent and recrystallization; IR (mineral oil): 3310–3250, and 1660 cm^{-1}.

β - Disulfones—*Bis(4-acetamidophenylsulfonyl)phenylmethane* (*II*a)—A 3.7 *M* solution of peracetic acid in methylene chloride (16.2 ml, 60 mmoles) was added to a suspension of I*a* (2.11 g, 5 mmoles) in 170 ml of dry methylene chloride over 15 min and the reaction mixture was stirred for 114 hr. The crystalline material removed by filtration gave II*a* after recrystallization; IR (mineral oil): 3350, 3310, 3280, 1670, 1315, and 1150 cm^{-1}.

Bis(4-aminophenylsulfonyl)phenylmethane (*II*b)—This compound was obtained by heating a suspension of II*a* in methanol and hydrochloric acid for 3 hr. When II*b* was recrystallized from methanol, the compound crystallized with solvent molecules, whereas using acetone as solvent would give pure II*b*; IR (mineral oil): 3460, 3360, 1320, and 1130 cm^{-1}.

Bis(phenylsulfonyl)-4-trichloromethylphenyl Methane (*II*c)—This compound was prepared by oxidation of I*c* by the method described for II*a*; IR (mineral oil): 1330, 1161, and 1150 cm^{-1}.

Bis(4-acetamidophenylsulfonyl)-4-trichloromethylphenyl Methane (*II*d)—This compound was prepared from I*d* by the method described for II*a*; IR (mineral oil): 3400, 1690, 1330, and 1150 cm^{-1}.

Bis(4-aminophenylsulfonyl)-4-trichloromethylphenyl Methane (*II*e)—Compound II*d* was acid hydrolyzed in hot ethanol and hydrochloric acid to give II*e* which was recrystallized; IR (mineral oil): 3460, 3390, 1310–1320, and 1135–1145 cm^{-1}.

4-Bis(phenylsulfonyl)methylbenzoic Acid (*III*f)—A 0.054 *M* aqueous solution of sodium hydroxide (74.5 ml, 4 mmoles) was added to a solution of II*c* (490 mg, 1 mmole) in 40 ml of tetrahydrofuran. The reaction mixture was stirred for 22 hr at ambient temperature. The tetrahydrofuran was removed under reduced pressure and the aqueous solution was extracted with two 30-ml portions of chloroform. The aqueous solution was acidified with 5% aqueous hydrochloric acid and extracted with two 30-ml portions of chloroform. The combined chloroform extracts were washed with water, dried over magnesium sulfate, and gave II*f* which was stirred with benzene; IR (mineral oil): 1690 cm^{-1}. Two recrystallizations of II*f* from acetonitrile gave a compound with mp 264–265°; IR (mineral oil): 3400 and 1730 cm^{-1}.

Anal.—Calc. for $C_{20}H_{16}O_7S_2$—C, 55.54; H, 3.73; S, 14.83. Found: C, 56.59, 56.35; H, 4.08, 3.87; S, 14.32.

Bis(benzylsulfonyl)-4-trichloromethylphenyl Methane (*III*b)—This was prepared from III*a* by the method described for II*a*; IR (mineral oil): 1320, 1150, and 1125 cm^{-1}.

4-Bis(benzylsulfonyl)methylbenzoic Acid (*III*c)—A 0.6 *M* aqueous solution of sodium hydroxide (20 ml, 12 mmoles) was added to a solution of III*b* (1.55 g, 3 mmoles) in 180 ml of tetrahydrofuran. The reaction mixture was stirred for 17 hr at ambient temperature. The organic solvent was removed under reduced pressure and the solution was acidified with 5% aqueous hydrochloric acid. Compound III*c* was extracted from the aqueous phase with chloroform and recrystallized.

Bis(phenylsulfonyl)-4-trichloromethylphenyl Chloromethane (*V*a)—A 5.25% aqueous solution of sodium hypochlorite (10 ml, 7 mmoles) was added to a solution of II*c* (490 mg, 1 mmole) in 25 ml of tetrahydrofuran. The solution was stirred at ambient temperature for 5 min and the organic layer yielded V*a* which was recrystallized; IR (mineral oil): 1350, 1330, 1320, and 1150 cm^{-1}.

Bis(4-acetamidophenylsulfonyl)-4-trichloromethylphenyl Chloromethane (*V*b)—This compound was prepared from II*d* and sodium hypochlorite by the method described for V*a*; IR (mineral oil): 3310, 3270, and 1670 cm^{-1}.

9,9-Bis(4-acetamidophenylsulfonyl)fluorene (*VII*b)—Oxidation of VII*a* by the method described for II*a* gave VII*b*; IR (mineral oil): 3310, 3280, 1670, 1350, and 1162 cm^{-1}. An attempt to prepare VII*b* from 9,9-dichlorofluorene and two molar equivalents of triethylammonium-4-acetamidophenyl sulfinate in acetonitrile yielded 90% of 9-fluorenone and 12% of IX*a* after heating the reaction mixture under reflux for 39 hr.

9,9-Bis(4-Aminophenylsulfonyl)fluorene (*VII*c)—This compound was prepared from VII*b* by acid hydrolysis in hot methanol and hydrochloric acid; IR (mineral oil): 3440, 3350, 1315, and 1150 cm^{-1}.

α-Chlorobenzyl Sulfones—*4-Acetamidophenyl-α-chlorobenzyl sulfone* (*IV*a)—A solution of triethylammonium-4-acetamidophenyl sulfinate (15 g, 50 mmoles), and benzal chloride (4.03 g, 25 mmoles) in 30 ml of *N,N*-dimethylformamide was heated at 100–105° for 46 hr. The reaction mixture was poured into 400 ml of water and the oily precipitate that formed hardened slowly. The IV*a* crystals were filtered after 24 hr, washed with water, and air dried; IR (mineral oil): 3360, 1700, 1325, and 1145 cm^{-1}.

4-Aminophenyl-α-chlorobenzyl Sulfone (*IV*b)—This compound was prepared from IV*a* by acid hydrolysis with 11.6 *M* aqueous hydrochloric acid at 100° for 17 hr; IR (mineral oil): 3400, 3450, 1295, and 1140 cm^{-1}.

4-Trichloromethylphenyl Phenylsulfonyl Chloromethane (*IV*c)—A solution of sulfuryl chloride (0.92 ml, 11.3 mmoles) in 60 ml of *n*-pentane was added to a boiling solution of Ic (3.44 g, 8.09 mmoles) in 100 ml of *n*-pentane during 1 hr (13). The reaction mixture was heated under reflux for an additional 2 hr. The *n*-pentane was removed under reduced pressure. The residue was dissolved in 200 ml of methylene chloride and a 1.59 *M* solution of peracetic acid in methylene chloride (61 ml, 97 mmoles) was added with stirring over 30 min. The reaction mixture was stirred at ambient temperature for 144 hr. The solution was concentrated under reduced pressure to 20 ml and white crystals precipitated upon addition of 5 ml of cyclohexane. The crystals were separated by filtration and washed with cyclohexane to give IV*c* which was recrystallized; IR (mineral oil): 1320 and 1150 cm^{-1}.

Derivatives of 4-Dichloromethylbenzoyl Chloride (X)—*4-Dichloromethylbenzanilide* (*VI*a)—This compound was prepared from a solution of X and aniline in benzene; IR (mineral oil): 3330 and 1640 cm^{-1}.

4'-Carboxy-4-dichloromethylbenzanilide (*VI*b)—This compound was prepared from a solution of X, 4-aminobenzoic acid, and pyridine in tetrahydrofuran; IR (mineral oil): 3310 and 1690–1640 cm^{-1}.

4-Acetamidophenyl-4-dichloromethyl Thiolbenzoate (*VI*c)—This compound was prepared from a solution of X, 4-acetamidothiophenol, and pyridine in tetrahydrofuran, IR (mineral oil): 3300 and 1660 cm^{-1}.

Derivatives of 4-Trichloromethylbenzoyl Chloride (XI)—*4-Trichloromethylbenzanilide* (*VI*d)—A solution of XI and aniline in tetrahydrofuran gave VI*d*; IR (mineral oil): 3310 and 1650 cm^{-1}.

4'-Nitro-4-trichloromethylbenzanilide (*VI*e)—A solution of XI, 4-nitroaniline, and triethylamine in acetonitrile gave VI*e*; IR (mineral oil): 3390 and 1670 cm^{-1}.

S-(Phenyl)-4-trichloromethyl Thiolbenzoate (*VI*f)—A solution of XI, thiophenol, and triethylamine in tetrahydrofuran gave VI*f*; IR (mineral oil): 1660 cm^{-1}.

S-(4-Acetamidophenyl)-4-trichloromethyl Thiolbenzoate (*VI*g)—A solution of XI, 4-acetamidothiophenol, and triethylamine in tetrahydrofuran gave VI*g*; IR (mineral oil): 3250 and 1660 cm^{-1}.

α-Disulfones and Thiolsulfonates—*Bis(4-acetylaminophenyl Sulfone)* (*VIII*a)—This was prepared (30) from 4-acetamidophenyl sulfinic acid and potassium permanganate, mp 245° [lit. (30) mp 245–250° dec.].

Bis(4-aminophenyl Sulfone) (*VIII*b)—Acid hydrolysis of VIII*a* in hydrochloric acid, methanol, and *N*-methyl-2-pyrrolidone at 100° for 2 hr gave VII*b*. Compound VIII*b* was recrystallized from a mixture of *N*-methyl-2-pyrrolidone and water, mp 215° dec. (31); IR (mineral oil): 3490, 3400, 1320, and 1125 cm^{-1}.

Anal.—Calc. for $C_{12}H_{12}N_2O_4S_2$; C, 46.14; H, 3.88; N, 8.97; S, 20.53. Found: C, 48.87; H, 4.10; N, 8.89; S, 20.39.

4'-Acetamidophenyl-4-acetamidobenzene Thiolsulfonate (*IX*a)—Compound I*a* (6.35 g, 15 mmoles) was suspended in 55 ml of acetic acid, and 30% hydrogen peroxide (8.55 g, 75 mmoles) was added during 30 min. The temperature of the reaction mixture was kept below 35° with occasional ice cooling during the addition of hydrogen peroxide. Stirring was continued for 37 hr. The suspension was poured into 450 ml of water and the undissolved material was filtered, and washed with water giving 4.34 g (81.5%) of IX*a*, mp 219–221° dec. Recrystallization from a mixture of *N,N*-dimethylformamide and water gave 3.22 g (59%) of IX*a*, mp 223–224° dec. [lit. (30) mp 236–237° dec.].

4'-Aminophenyl-4-aminobenzene Thiolsulfonate (*IX*b)—This compound was prepared by acid hydrolysis of IX*a* in hydrochloric acid and methanol, mp 185–186° dec. [lit. (30) mp 183°].

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GLC Analysis of Trifluoperazine in Human Plasma

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Abstract □ This report describes a sensitive gas chromatographic procedure for the measurement of trifluoperazine in human plasma. Trifluoperazine was extracted into heptane–2-propanol by a two-step procedure and analyzed directly without derivatization. Prochlorperazine was employed as an internal standard because its structural and extraction characteristics were similar to trifluoperazine. The use of a nitrogen detection system reduced the number of interfering peaks. The within-day coefficient of variation in the method, over a 0.2–20-ng/ml concentration range was 9.4%.

Keyphrases □ Trifluoperazine—gas chromatographic measurement in human plasma □ Gas chromatography—measurement of trifluoperazine in human plasma □ Tranquilizers—trifluoperazine, gas chromatographic measurement in human plasma

The relationship between plasma concentrations of various psychoactive drugs and their clinical effects was recently discussed (1, 2). It was shown that drug concentrations can vary widely among patients receiving identical doses (3–6). Based on such interindividual variations in plasma levels of psychoactive drugs, it was suggested that

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